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Published <i>With international search report.</i>																																									
(54) Title: 110 HUMAN SECRETED PROTEINS																																									
(57) Abstract <p>The present invention relates to novel human secreted proteins and isolated nucleic acids containing the coding regions of the genes encoding such proteins. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human secreted proteins. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human secreted proteins.</p>																																									

The tissue distribution in testis indicates polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, treatment, and/or prevention for abnormalities of the reproductive system. In addition, expression of this gene product in the testis may implicate this gene product in normal testicular function. This gene product may be useful in the treatment of male infertility, and/or could be used as a male contraceptive. Moreover, the protein product of this gene may be useful in the treatment, detection, and/or prevention of a variety of disorders related to androgen-regulated tissues, particularly the prostate gland. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:12, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

The translation product of this gene shares sequence homology with the human VAKTI precursor (See Genbank Accession No. gnlIPIDle1311078 (AJ228139)), in addition to the ovoinhibitor and thrombin inhibitors, which are thought to be important in inhibition of protease activities. Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of monocytes to calcium. Thus, it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both immune cells, in addition to other cell-lines or tissue cell types. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocytes. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule concentration can be measured to identify supernatants which bind to

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NO:272). WIGLFSLVQASFPFLTFRYSLQSSAYE (SEQ ID NO:273), NSAVN
IKIRQRM EYFSVPEKMTLFVVQMGKCMATCVPCVKPTSKQKMKKRKRLKHE
LETKENLEKQPHMQSFAVNIESL (SEQ ID NO:274), IKIRQRM EYFSVPEKMTL

FVVQM (SEQ ID NO:275), and/or VKPTSKQKMKKRKRLKHELETKENL (SEQ ID NO:276). Polynucleotides encoding these polypeptides are also encompassed by the invention. The gene encoding the disclosed cDNA is believed to reside on chromosome 5. Accordingly, polynucleotides related to this invention are useful as a marker in linkage analysis for chromosome 5.

This gene is expressed primarily in heart, tonsils, Hodgkin's lymphoma, neuroblastoma, leukocyte and lung.

Therefore, polynucleotides and polypeptides of the invention are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cardiovascular, immune, or hemodynamic disorders. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, muscle, immune, hematopoietic, pulmonary, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, pulmonary surfactant or sputum, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

Preferred epitopes include those comprising a sequence shown in SEQ ID NO:127 as residues: Ala-20 to Gln-27.

The tissue distribution in heart and immune cells and tissues, the homology to protease inhibitors, in addition to the detected calcium flux, EGR1, and GAS biological activities indicates polynucleotides and polypeptides corresponding to this gene are useful for diagnosis and treatment of hemodynamic or vascular disorders, including hemorrhage, heart failure, and embolism, because proteases and their inhibitors are often involved in the cascades controlling hemodynamic controls. Protein may also show utility in the treatment, detection, and/or prevention of a variety of metabolic (i.e., cellular or physiological) and/or proliferative disorders in which aberrant regulation of a protease is thought to be involved, particularly in the premature activation of zymogens, for example. The secreted protein can also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions and as nutritional supplements. It may also have a very wide range of biological activities. Typical of these are cytokine, cell proliferation/differentiation modulating activity or induction of other cytokines:

immunostimulating/immunosuppressant activities (e.g. for treating human immunodeficiency virus infection, cancer, autoimmune diseases and allergy); regulation of hematopoiesis (e.g. for treating anemia or as adjunct to chemotherapy); stimulation or growth of bone, cartilage, tendons, ligaments and/or nerves (e.g. for treating wounds, stimulation of follicle stimulating hormone (for control of fertility); chemotactic and chemokinetic activities (e.g. for treating infections, tumors); hemostatic or thrombolytic activity (e.g. for treating hemophilia, cardiac infarction etc.); anti-inflammatory activity (e.g. for treating septic shock, Crohn's disease); as antimicrobials; for treating psoriasis or other hyperproliferative diseases; for regulation of metabolism, and behavior. Also contemplated is the use of the corresponding nucleic acid in gene therapy procedures. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence is cumbersome.

Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2303 of SEQ ID NO:13, b is an integer of 15 to 2317, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

The translation product of this gene shares sequence homology with the ecotropic retrovirus receptor and the human cationic amino acid transporter-3 (See Genbank Accession No. gnlIPIDe1198517) which are thought to be important in viral infections and amino acid and polyamine transport. In specific embodiments, polypeptides of the invention comprise the following amino acid sequence:

PRVRGTVVRLRQHRPSAYILVSTVLTL MVPWHS LDPDSALADAFYQRGYRWAG
 FIVAAGSICA (SEQ ID NO:277), TVVRLRQHRPSAYILVSTVLTL MVP (SEQ ID
 NO:278), WHSLDPDSALADAFYQRGYRWAGFIV (SEQ ID NO:279), TPSCSASS
 SPCHALSMPWPPMGSSSRCLPMCTPGHRCLWRAPWRSGSSRPSWHCCWTWS

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gcctcccagg	acagccagca	cagcccccca	cacgtccgag	cccacctcct	catttccccg	540
cttcccgcgt	tcccaagcat	gggaggacct	gccggacgca	gcgcaccaty	tytctaaca	600
gagaccaagt	ctgagcttca	acgcttgccg	agacgacagg	cacgtgcaag	cytytcytyt	660
ccagcaggag	agcccggagc	aggacacagc	gaytctttca	actgcgtccc	gacaaacggt	720
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cgacgactag	cccttaaaag	aggctggagc	ccctgaggaa	gcgggtcttt	aggcaaaacc	1380
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<212> DNA

<213> Homo sapiens

<220>

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<223> n equals a,t,g, or c

<220>

<221> SITE

<222> (2165)

<223> n equals a,t,g, or c

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 65 70 75 80
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 85 90 95
 Lys Pro Cys Trp Arg Pro Gly Gly Gln Ala Arg Xaa Leu Gly Ser Trp
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 35 40 45
 Lys Phe Phe Gln Ser Leu Asp Gly Ile Met Phe Ile Asn Lys Cys Ala
 50 55 60
 Thr Cys Lys Met Ile Leu Glu Lys Glu Ala Lys Ser Gln Lys Arg Ala
 65 70 75 80
 Arg His Leu Ala Arg Ala Pro Lys Ala Thr Ala Pro Thr Glu Leu Asn
 85 90 95
 Cys Asp Asp Phe Lys Lys Gly Glu Arg Asp Gly Asp Phe Ile Cys Pro
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 Asp Tyr Tyr Glu Ala Val Cys Gly Thr Asp Gly Lys Thr Tyr Asp Asn
 115 120 125
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 130 135 140
 Val Lys Ser Glu Gly Glu Cys Lys Ser Ser Asn Pro Glu Gln Asp Val
 145 150 155 160

74

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Arg Glu Asn Asp Pro Val Leu Gly Pro Asp Gly Lys Thr His Gly Asn	180	185	190
Lys Cys Ala Met Cys Ala Xaa Leu Xaa Xaa Lys Glu Ala Glu Asn Ala	195	200	205
Lys Arg Glu Gly Glu Thr Arg Ile Arg Arg Asn Ala Glu Lys Asp Phe	210	215	220
Cys Lys Glu Xaa Glu Lys Gln Val Arg Asn Gly Arg Leu Phe Cys Thr	225	230	235
Arg Glu Ser Asp Pro Val Arg Gly Pro Asp Gly Arg Met His Gly Asn	245	250	255
Lys Cys Ala Leu Cys Ala Glu Ile Phe Lys Gln Arg Phe Ser Glu Glu	260	265	270
Asn Ser Lys Thr Asp Gln Asn Leu Gly Lys Ala Glu Glu Lys Thr Lys	275	280	285
Val Lys Arg Glu Ile Val Lys Leu Cys Ser Gln Tyr Gln Asn Gln Ala	290	295	300
Lys Asn Gly Ile Leu Phe Cys Thr Arg Glu Asn Asp Pro Ile Arg Gly	305	310	315
Pro Asp Gly Lys Met His Gly Asn Leu Cys Ser Met Cys Gln Ala Tyr	325	330	335
Phe Gln Ala Glu Asn Glu Glu Lys Lys Lys Ala Glu Ala Arg Ala Arg	340	345	350
Asn Lys Arg Glu Ser Gly Lys Ala Thr Ser Tyr Ala Glu Leu Cys Ser	355	360	365
Glu Tyr Arg Lys Leu Val Arg Asn Gly Lys Leu Ala Cys Thr Arg Glu	370	375	380
Asn Asn Pro Ile Gln Gly Pro Asp Gly Lys Val His Gly Asn Thr Cys	385	390	395
Ser Met Cys Glu Val Phe Phe Gln Ala Glu Glu Glu Glu Lys Lys Lys	405	410	415
Lys Glu Gly Xaa Ser Arg Asn Lys Arg Gln Ser Lys Ser Thr Ala Ser	420	425	430
Phe Xaa Glu Leu Cys Ser Glu Xaa Arg Lys Ser Arg Lys Asn Gly Arg	435	440	445
Leu Phe Cys Xaa Arg Glu Asn Asp Pro Ile Gln Gly Pro Asp Gly Lys	450	455	460

75

Met His Gly Asn Thr Cys Ser Met Cys Glu Ala Phe Phe Gln Gln Glu
 465 470 475 480

Glu Arg Ala Arg Ala Lys Ala Lys Arg Glu Ala Ala Lys Glu Ile Cys
 485 490 495

Ser Glu Phe Arg Asp Gln Val Arg Asn Gly Thr Leu Ile Cys Thr Arg
 500 505 510

Glu His Asn Pro Val Arg Gly Pro Asp Gly Lys Met His Gly Asn Lys
 515 520 525

Cys Ala Met Cys Ala Ser Val Phe Lys Leu Glu Lys Lys Lys Lys Lys
 530 535 540

Lys Lys Lys Lys Lys Gly Arg Pro Leu Xaa
 545 550

<210> 128

<211> 308

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (308)

<223> Xaa equals stop translation

<400> 128

Met Asn Thr Val Leu Leu Ser Leu Leu Phe Ser Leu Pro Arg Ile Val
 1 5 10 15

Tyr Ala Met Ala Ala Asp Gly Leu Phe Phe Gln Val Phe Ala His Val
 20 25 30

His Pro Arg Thr Gln Val Pro Val Ala Gly Thr Leu Ala Phe Gly Leu
 35 40 45

Leu Thr Ala Phe Leu Ala Leu Leu Asp Leu Glu Ser Leu Val Gln
 50 55 60

Phe Leu Ser Leu Gly Thr Leu Leu Ala Tyr Thr Phe Val Ala Thr Ser
 65 70 75 80

Ile Ile Val Leu Arg Phe Gln Lys Ser Ser Pro Pro Ser Ser Pro Gly
 85 90 95

Pro Ala Ser Pro Gly Pro Leu Thr Lys Gln Gln Ser Ser Phe Ser Asp
 100 105 110

His Leu Gln Leu Val Gly Thr Val His Ala Ser Val Pro Glu Pro Gly
 115 120 125

Glu Leu Lys Pro Ala Leu Arg Pro Tyr Leu Gly Phe Leu Asp Gly Tyr
 130 135 140